Examiner's suggestion to define claim 2 as a method for monitoring septic shock. The method defined in claims 2-8 of the present invention relates to the treatment of septic shock and therefore, claims 2-8 should not be withdrawn.

As for claims 14-17, neutrophil infiltration during inflammatory conditions is caused by septic shock, see page 3, lines 4-5 of the present application. Therefore, claims 14-17 relate to the treatment of septic shock and should not be withdrawn. In support of this argument, Applicants have amended claim 14 to define "a method for controlling neutrophil infiltration during inflammatory conditions caused by septic shock by administering to a subject in need thereof a pharmacologically effective dose of curcumin." Support for claim 14 can be found in original claim 14 and on page 3, lines 4-5 of the present application.

Claim 1 has been cancelled.

The amendments to the claims are not narrowing and are made to expedite the prosecution by eliminating prolonged arguments over matters that are not of concern to our client regarding the patent application and are not directed to the patentability of the claims. They should therefore have no effect on the application of the doctrine of equivalents to the newly amended claims.

Specification Objection

As suggested by the Examiner, the last paragraph on page 8 of the present application has been replaced so that the spacing of the lines are double spaced.

Claim Rejection - 35 U.S.C. 102

The 35 U.S.C. 102(b) rejection is no longer applicable due to the cancellation of claim 1 of the present invention.

Claim Rejection 35 U.S.C. 103(a)

Claims 9-13 were rejected under 35 U.S.C. 103(a) as being unpatentable over Aggarwal (WO 9709877) in view of Schneider (U.S. Patent No. 6,013,273).

The Examiner alleges that it would have been obvious to incorporate the teachings of Aggarwal with Schneider et al. who teaches the use of antioxidant in treating septic shock.

To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art, *In re Royka*, 490 F.2d 981, USPQ 580 (CCPA 1974).

The present invention relates to method for the treatment of septic shock conditions comprising administering to a subject in need thereof orally at specified time intervals a dosage of curcumin in the range of from 40 mg/kg to 60 mg/kg of body weight which is effective to prevent neutrophil infiltration from blood vessels to underlying tissues.

The present invention also relates to a method for treating septic shock conditions

in an animal wherein the method comprises administering orally a pharmacologically effective dose of curcumin to the animal; observing every two to three hours for septic shock and probing reduction in neutrophil infiltration from blood vessels to the underlying tissue by staining and microscopically examining the extent of inflammation.

The oral administration of curcumin at the defined dosages has the unexpected effect of preventing neutrophil infiltration from blood vessels to underlying tissues. Neutrophil infiltration results from the cumulative effect of many mediators acting together and is a primary step leading to organ damage during inflammatory conditions, please see the last paragraph on page 4 of the previous response for a description of the many mediators. Applicants have devised an *in vivo* method for the treatment of septic shock by preventing neutrophil infiltration from blood vessels to underlying tissues. This is a novel and important part of the finding wherein the inventors provide evidence for the first time and demonstrate *in vivo* that curcumin prevents infiltration of neutrophils to the underlying tissues and subsequently prevents organ damage.

The Examiner admits that the Aggarwal reference does not describe preventing neutrophil infiltration from blood vessels to underlying tissues or oral administration of curcumin in specific time intervals.

Aggarwal has only shown inhibition of the TNF-α induced activation of NF-κB in a transformed cell line ML-1α cell line *in vivo* and has extrapolated it to the prevention of septic shock *in vivo*.

There is no teaching or suggestion in Aggarwal that inhibiting the activation of the NF-κB transcription factor *in vitro* would effectively prevent neutrophil infiltration from blood vessels to underlying tissues.

An animal is an organism composed of various cell types and multiple biochemical pathways that operate together to determine the pathophysiological state. Inhibiting the activation of the NF-κB transcription factor as described in Aggarwal occurs *in vitro* and where there are biochemical pathways and feedback mechanisms, the inhibition may not necessarily be accomplished in an *in vivo* environment.

Attached is a sworn affidavit by Balaram Ghosh, an inventor of the present invention, describing the administration of curcumin to prevent neutrophil infiltration. As stated in the affidavit, pharmacologically effective doses of curcumin were administered orally to female Swiss albino mice in a suspension comprising a non-toxic organic solvent or oil at various times prior to and after injection of LPS. As explained in the present application, LPS was administered to animals to induce symptoms of septic shock. LPS is at the top of the cascade of septic shock events, whereas TNF-α and NF-κB, as described in Aggarwal, are only one of the many mediators in the lower layers of the regulatory cascade.

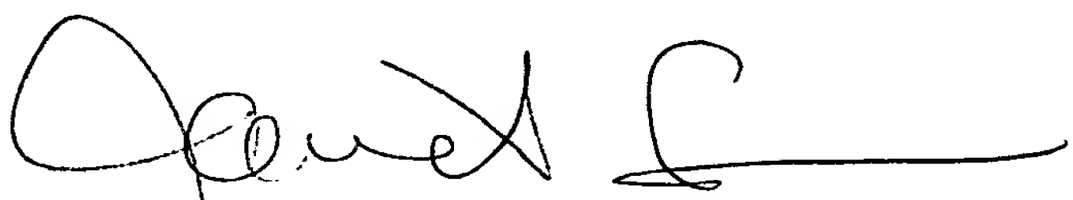
It was determined that the administration of curcumin at the dosages specified have the unexpected effect of preventing neutrophil to underlying blood vessels and underlying tissues, see paragraphs 3 and 4 of the sworn affidavit.

This finding is not obvious from Aggarwal.

The Examiner relies on Schneider to teach the use of an antioxidant in treating septic or endotoxin shock. Schneider does not correct the deficiencies of the primary reference and therefore claims 9-14 of the present invention are nonobvious in light of the cited prior art.

In light of the above, Applicants submit that all rejections and objections of record have been overcome. Applicants accordingly submit that the application is now in condition for allowance and respectfully request action in accordance therewith.

Respectfully submitted,



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14. (Amended) A method for controlling neutrophil infiltration during inflammatory conditions caused by septic shock by administering to a subject in need thereof a pharmacologically effective dose of curcumin.

AFFIDAVIT OF.....*BALARAM GHOSH*.... AGED ABOUT .... 47 Years, S/o MR SIBARAM GHOSH.....RESIDENT OF B114, SHAKTI APARTMENTS, SECTOR-9, ROHINI, DELHI 110085. And of Council of Scientific and Industrial Research, New Delhi, India.

I, the above named deponent, do hereby solemnly affirm and declare as follows:

1. I am an inventor in respect of US Patent application No. 09/535,390 filed on March 24, 2000 relating inter alia, to an invention for the treatment of septic shock lethality using curcumin.

2. I am advised that I am required to affirm that the results obtained in the invention are true.

3. I hereby affirm that the administration of curcumin at the dosages specified in the patent application have the previously unexpected effect of preventing neutrophil infiltration from blood vessels to underlying tissues.

4. I also affirm that curcumin was administered in the following dosages and in the manner specific below and prevented the infiltration of neutrophils to underlying blood vessels.

5. DETAILS OF ADMINISTRATION:
Age-and body weight-matched (25-30 g) female swiss albino mice were fed orally with curcumin in the range of 40 mg/kg to 60 mg/kg body weight. Pharmacologically effective dose of curcumin was administered orally as suspension in non-toxic organic solvent or oil at various times prior to and after injecting LPS (40mg/kg). The mice were fed with curcumin 4 h and 2 h prior to, simultaneously and at time intervals of 4 , 16 , 24 , 48 and 72 hours after injecting LPS. The mice were alternatively fed with curcumin at time intervals of 3 , 6 , 9, 24 and 42 hours after

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K. Srivastava
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injecting LPS. The mice were alternatively fed with curcumin at time intervals of 3 , 6 , 9, 24 and 42 hours after injecting LPS. The pharmacologically effective dose of curcumin was alternatively administered orally alongwith an antioxidant preparation.

6. I affirm that no part of what is stated above is false.

DEPONENT

VERIFICATION:
Verified at New Delhi on this ~~29th~~ 3rd day of ~~November~~ December 2002 that the contents of my above affidavit are true to my knowledge and belief and that nothing material or relevant has been concealed therefrom.

DEPONENT

ATTESTED

Notary Public Delhi

4 DEC 2002

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